

Applicants: Kenneth A. Jones, et al.  
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to applicants' right to pursue the subject matter of these claims in a continuation or divisional application.

Please amend claim 159 to read as follows:

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C1 --159. (Amended) The DNA of claim 157, wherein the DNA is genomic DNA and consists of nucleotides encoding the chimeric G protein.--

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A marked-up version of the amendments showing the changes made is attached hereto as **Exhibit A**.

#### REMARKS

Claims 77, 141 and 156-183 were pending in the subject application. Claims 77 and 141 are withdrawn from consideration. By this Amendment, applicants have canceled claims 77 and 141 without disclaimer or prejudice; and amended claim 159. Accordingly, upon entry of this Amendment, claims 156-183, as amended, will be pending and under examination.

Support for claim 159 may be found inter alia in the specification, as originally-filed, on page 30, line 27; and page 29, lines 34-35.

Accordingly, applicants respectively request that the Amendment be entered.

#### A. Rejection under 35 U.S.C. §112, first paragraph

1. On page 2 of the November 19, 2002 Office Action the Examiner rejected claim 159 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in

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the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in Paper 8, entered February 8, 2002 as applied to previous claim 6.

The Examiner alleged that due to the limitation of "genomic DNA" recited in the claim, a determination of what the claim as a whole covers indicates that elements which are not particularly described, for example promoters, enhancers, untranslated regions and introns, are encompassed by this claim. The Examiner then alleged that there is no actual reduction to practice of the claimed invention, or complete description of the structure. The Examiner then alleged that a biomolecular sequence described only by a functional characteristic, in this case an isolated genomic nucleic acid encoding a chimeric G protein, without any known or disclosed correlation between function and the structure of the sequence is not a sufficient identifying characteristic. (Examiner cites University of California v. Eli Lilly and Co. 43 USPQ2d at 1406.) The Examiner also alleged that there is no known or disclosed correlation between this function and the structure of the non-described regulatory elements and untranslated regions of the genomic DNA.

The Examiner concluded that one skilled in the art would not recognize from the disclosure that the Applicants were in possession of the claimed invention. The Examiner also alleged that contrary to Applicants' previous arguments, this claim does not only cover the coding sequence, it still encompasses elements which are not particularly described, e.g. promoters, enhancers, untranslated regions and introns, thus the rejection is maintained.

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In order to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have amended claim 159 to now recite:

"The DNA of claim 157, wherein the DNA is genomic DNA and consists of nucleotides encoding the chimeric G protein".

Applicants point out that the MPEP § 2111.03 recite:

"The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim."

Applicants maintain that claim 159, as amended, only encompasses the coding region of the chimeric G protein. Applicants maintain that the recitation "nucleotides encoding" would be interpreted by a person of ordinary skill in the art to mean only those nucleotides that are translated into amino acids (the chimeric G protein). Therefore, applicants maintain that the claim does not encompass elements which are not translated into the chimeric G protein, e.g. promoters, enhancers, untranslated regions (UTR's), and introns.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this portion of the rejection.

2. On page 4 of the November 19, 2002 Office Action the Examiner rejected claims 156-183 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in Paper No. 8, entered February 8, 2002, as applied to previous claims 1-22.

The Examiner alleged that these are genus claims. The Examiner

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alleged that according to the specification, the term variant means a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to SEQ ID NO: 1. The Examiner then alleged that the specification and claim do not indicate what distinguishing attributes are shared by the members of the genus. The Examiner then alleged that the specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 1. The Examiner concluded that the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted.

In response, applicants point out that 35 U.S.C. §112, first paragraph, states that "[t]he specification shall contain a *written description* of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, ..." (emphasis added).

The first paragraph of §112 "requires a 'written description of the invention' which is separate and distinct from the enablement requirement. ... [T]he applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (emphasis in original).

An applicant can show possession of a claimed invention "by describing the claimed invention with all of its limitations

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using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the claimed invention." M.P.E.P. 2163(I), citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Consistent with this notion is that "[a]n adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the invention." M.P.E.P. 2163(II) (A) (3) (a). (Emphasis added.)

Applicants maintain that the claimed invention describes an isolated nucleic acid encoding a chimeric G protein, wherein the chimeric G protein comprises an invertebrate Gαq G protein from which at least five, but not more than twenty-one, contiguous amino acids beginning with the C-terminal amino acid have been deleted and replaced by a number of contiguous amino acids present in a vertebrate G protein beginning with the C-terminal amino acid of such vertebrate G protein, wherein such number equals the number of amino acids deleted; provided that the chimeric G protein, upon activation, produces a Gαq second messenger response.

Applicants point out that the specification and claim teach the skilled artisan to delete a number of contiguous amino acids from the C-terminal end of the invertebrate Gαq G protein and replace the number of amino acids deleted with the same number of amino acids from the C-terminal end of a vertebrate G protein.

In response to the Examiner's allegation on page 4 of the November 19, 2002 Office Action which states that the specification and claim do not place any limit on the number of

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amino acid substitutions, deletions, insertions, and or additions that maybe made, applicants note that the specification teaches on page 30, lines 14-22 that the number of amino acids that can be deleted and replaced in any given sequence can be no less than 5 and no more than 21 amino acids, thereby limiting the scope of the claim. The claim is further limited in that the number of amino acids replaced must equal the number of amino acids deleted. See page 30, lines 22-23 of the specification as originally filed.

The specification further teaches the methods to construct chimeric G proteins at page 68, lines 9-23, as well as specific examples of primers used to construct representative examples chimeric G proteins in Tables 1-3. The specification clearly outlines the following steps on page 68, lines 9-23: 1) primers are designed for use in PCR to amplify the 3' end of the appropriate template gene and numerous examples of primer sequences are given in Table 1; 2) the PCR product of step 1 is isolated and subcloned back into the full length chimeric gene using routine methods known to those skilled in the relevant art (specific examples, including 4 specific invertebrate Gαq examples are given in Table 2); and 3) the PCR derived sequences are verified by sequence analysis.

An alternate method of constructing chimeric Gαq proteins is also described, i.e. the Quikchange site-directed mutagenesis kit which can be purchased from Stratagene. See page 68, lines 19-20 of the specification. Two specific invertebrate constructs were actually made using this method and are disclosed in Table 3.

The specification on page 32, lines 9-17 further describes many examples of invertebrate Gαq G proteins useful in the practice

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of the subject invention, including *C. elegans* Gαq, *D. melanogaster* Gαq, *L. polyphemus* Gαq, *P. yessoensis* Gαq, *L. forbesi* Gαq, *H. americanus* Gαq, *L. stagnalis* Gαq, *G. cydonium* Gαq, and *D. discoideum* Gα4 G proteins. See also Figures 5A-5B. These invertebrate Gαq sequences can be used as the template in the method on page 68 of the specification as outlined above.

Figure 1 of the specification' also provides examples of vertebrate G proteins including human Gα4, mouse Gα16, human Gα16, human Gα11, bovine Gα11, mouse Gα11, turkey Gα11, *Xenopus* (African frog) Gα11, mouse Gα14, and bovine Gα14. The sequence information of these vertebrate G proteins can be used to design primers in order to achieve the chimeric 3' end as described in the method on page 68 and outlined above.

Following the teachings at page 68, lines 9-23 and Tables 1-3 and given the sequence information of template invertebrate cDNA and PCR primers corresponding to vertebrate G proteins, an artisan of ordinary skill can make many combinations of chimeric G proteins commensurate in scope with the now pending claims.

The Examiner has erroneously stated that applicants have only taught chimeric Gαq proteins comprising human Gαq/z5, *C. elegans* Gαq/z5 and *C. elegans* Gαq/z9. In fact, Figure 2A-2B describes SIX examples of the claimed invention, namely chimeras that were constructed comprising an invertebrate Gαq G protein "backbone" and vertebrate C-terminal portion. These six examples are *C. elegans* Gαq/z5, *C. elegans* Gαq/z9, *C. elegans* Gαq/s9, *C. elegans* Gαq/s21, *C. elegans* Gαq/i3(5) and *D. melanogaster* Gαq/z5.

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SEQ ID NO:1 describes ***C. elegans* Gαq/z5**, a G protein chimera comprising a *C.elegans* Gαq G protein with the C-terminal portion replaced with 5 amino acids of vertebrate Gαz. SEQ ID NO: 2 describes ***C. elegans* Gαq/z9**, a *C.elegans* Gαq G protein with the C-terminal portion replaced with 9 amino acids of vertebrate Gαz. SEQ ID NO:3 describes ***C. elegans* Gαq/s9**, a *C.elegans* Gαq G protein with the C-terminal portion replaced with 9 amino acids of vertebrate Gαs. SEQ ID NO:4 describes ***C. elegans* Gαq/s21**, a *C.elegans* Gαq G protein with the C-terminal portion replaced with 21 amino acids of vertebrate Gαs. SEQ ID NO:5 describes ***C. elegans* Gαq/i3(5)**, a *C.elegans* Gαq G protein with the C-terminal portion replaced with 5 amino acids of vertebrate Gαi3. SEQ ID NO:41 describes ***D. melanogaster* Gαq/z5**, a *D.melanogaster* Gαq G protein with the C-terminal portion replaced with 5 amino acids of vertebrate Gαz.

The specification specifically teaches how to make further examples of chimeric G proteins. Following the teachings of SEQ ID NO:4, i.e. *C. elegans* Gαq/s21 (which corresponds to *C.elegans* Gαq G protein with the C-terminal portion replaced with 21 amino acids of vertebrate Gαs), and using the C-terminal portion of Gαz as given in SEQ ID NO:38, the skilled artisan can easily construct ***C. elegans* Gαq/z21**. Similarly, following the teachings of SEQ ID NO:4, i.e. *C. elegans* Gαq/s21, and using the C-terminal portion of Gαi3 as given in SEQ ID NO:40, the skilled artisan can easily construct ***C. elegans* Gαq/i3(21)**.

Given the teachings of the specification which provides a representative number of examples, applicants maintains that the



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specification of this application containing a sufficient written description. Contrary to the Examiner's allegations on page 5 on the November 19, 2002 Office Action, applicants have disclosed a representative number of examples. Applicants have also disclosed the relevant identifying characteristics of the genus, i.e. the portions of the nucleic acid that make up the chimeric G protein encompassed by the claims. Applicants have described methods to construct chimeric G proteins, and has provided numerous different portions that can be combined to make chimeric G proteins encompassed by the claim.

Furthermore, the specification describes methods for transfecting cells with such chimeric Gαq G proteins, and also various G protein-coupled receptors, for the purpose of verifying their function. See page 71, line 1 through page 73, line 14. The methods for determining functional activity, i.e. the second messenger response elicited by a functioning Gαq G protein, i.e. intracellular calcium mobilization and inositol phosphate, is described on page 78, line 6 through page 80, line 27.

Applicants maintain that the specification provides an adequate written description for the invention as claimed. That is, the specification conveys with reasonable clarity that applicants were in possession of the instant invention at the time the subject application was filed.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**B. Rejection under 35 U.S.C. §112, second paragraph**

On page 6 of the November 19, 2002 Office Action the Examiner rejected claims 156-176 and 179-183 under 35 U.S.C. §112, second

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paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner alleged that claim 156 is vague and indefinite in the recitation of "producing a  $G\alpha q$  second messenger response". The Examiner pointed out that the specification on page 29, lines 1-4 defines a " $G\alpha q$  second messenger response" as "one of a number of responses which are typically produced by activation of G protein heterotrimers containing  $G\alpha q$ ." The Examiner then pointed out that G proteins upon activation bind to effectors which produce the second messenger response. The Examiner alleged that it is not clear from the claim whether the chimeric  $G\alpha q$  protein binds to an effector and induces a second messenger response, or whether the chimeric  $G\alpha q$  protein produces a second messenger response itself.

Applicants maintain that claim 156 recites that the chimeric G protein retains the function of a  $G\alpha q$  protein. Although the Examiner questioned whether the chimeric  $G\alpha q$  protein 1) binds to an effector *then* induce a second messenger response, or 2) produces a second messenger response itself in some manner. Applicants maintain that the recitation is clear in light of the description and the knowledge of the skilled person.

As noted by the Examiner, the specification on page 29, lines 1-4 teaches that a  $G\alpha q$  second messenger response is one of a number of responses which are typically produced by activation of G protein heterotrimers containing  $G\alpha q$ . The specification further teaches that a typical response is the activation of phospholipase C isoforms. See the specification on page 3, lines

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1-12. The specification also teaches that beta-gamma sub-units released from an Gαq protein may interact with a number of effectors. See page 85, lines 18-24.

It is well known that Gαq proteins activate the described effectors which in turn initiate second messenger responses that are routinely measured by the person skilled in the art. Numerous second messenger assays, i.e. functional assays, are described in detail in the specification on page 75, line 30 through page 85, line 24. In light of the teachings of the instant specification and the knowledge of the skilled person, applicants maintain that claim 156 clearly defines the function of the chimeric G protein as one which produces a Gαq second messenger response.

Accordingly, applicants maintain that contrary to the Examiner's allegations, claims 156-176 and 179-183 clearly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

#### **C. Rejection under 35 U.S.C. §103**

On page 7 of the November 19, 2002 Office Action the Examiner rejected claims 156-183 under 35 U.S.C. §103(a) as allegedly being unpatentable over Conklin et al in view of Milligan et al. (1999) and further in view of Silva et al. (1990).

The Examiner alleged that Conklin et al. teaches that specific amino acid residues at the C-termini of alpha subunits can determine the abilities of individual G proteins to discriminate among specific subsets of receptors (page 27, column 2, first paragraph). The Examiner alleged that Conklin et al. replaced C-

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terminal amino acids of alpha q with the corresponding residues of alpha i2 to create alpha q/i2 chimeras that can mediate stimulation of phospholipase C by receptors otherwise coupled exclusively to Gi (page 274, Figure 1). The Examiner also alleged that Conklin et al. also made chimeras in which the last five residues of Gαq were replaced by the corresponding amino acids of αz and αo (page 275, Figure 3a).

The Examiner then acknowledged that Conklin does not teach DNA encoding an invertebrate Gαq protein.

The Examiner then alleged that Milligan teaches that a wide range of chimaeric alpha subunits have been produced in order to design a universal ligand-screening systems such that any GPCR can be screened using a common assay end-point. The Examiner then alleged that Milligan teaches the use of chimeric yeast/mammalian G proteins.

The Examiner then acknowledged that Milligan does not teach chimeric Gαq proteins from *C. elegans*.

The Examiner further alleged that Silva et al. teaches the cloning of a G protein α-subunit gene and that nematodes are useful for studying G protein mutants, since they are less likely to be lethal. The Examiner then alleged that it would have been obvious to one of skill in the art at the time the invention was made to make a chimeric Gα subunit as taught by Conklin et al. comprising a sequence from a nematode, as taught by Silva et al. The Examiner alleged that the motivation is provided in Milligan et al. who teaches that chimeric G protein alpha subunits need to be produced in order to design universal ligand-screening systems.

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In response, applicants maintain that claim 156, the sole independent claim, recites:

"An isolated nucleic acid encoding a chimeric G protein, wherein the chimeric G protein comprises an invertebrate G $\alpha$ q G protein from which at least five, but not more than twenty-one, contiguous amino acids beginning with the C-terminal amino acid have been deleted and replaced by a number of contiguous amino acids present in a vertebrate G protein beginning with the C-terminal amino acid of such vertebrate G protein, wherein such number equals the number of amino acids deleted; provided that the upon activation chimeric G protein produces a G $\alpha$ q second messenger response."

The Examiner has acknowledged that Conklin et al., the primary reference, fails to teach DNA encoding an invertebrate G $\alpha$ q protein. Applicants note that the notion of deleting not less than 5, not more than 21 amino acids from an invertebrate G $\alpha$ q protein is an essential feature of the claimed invention.

Applicants maintain that Conklin et al. does not suggest or motivate one skilled in the art to make applicants' invention. Conklin et al. does not recognize or teach that vertebrate and invertebrate G $\alpha$ q proteins have different structures and that the latter supports a universal assay system which is capable of functioning with G $\alpha$ i/o-, G $\alpha$ s-, and G $\alpha$ q-coupling receptors. (See the application on page 89, lines 5-12.) In fact, the mammalian assay system taught by Conklin et al. is not universal for G $\alpha$ s-coupled receptors. Applicants note that Conklin acknowledges that he has failed to identify an assay system for G $\alpha$ s-coupled receptors on page 275, paragraph 2, lines 4-7, which state: "[a] chimaera in which the last five residues of  $\alpha$ q were replaced with the corresponding amino acids of  $\alpha$ s did not allow G $\alpha$ s-coupled receptors to stimulate PLC (data not shown)." Conklin was not able to enhance promiscuity of the G $\alpha$ q-subunit for use in a

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"universal" assay system.

Milligan et al., the reference that the Examiner alleged provides the motivation, explores the use chimaeric G proteins with a Gq-backbone, Gi-backbone, or Gs-backbone; or yeast G protein (Gpa1). Milligan concludes "...it is impossible to predict *a priori* the likelihood of a particular GPCR interacting effectively with any specific chimaeric G protein  $\alpha$  subunit." (Page 124, column 1, first paragraph.) (Milligan does not suggest whether a Gq, Gi, Gs or Gpa1 assay system would be the best method for making chimaera.) In fact, Milligan states "[t]he 'universal' G proteins G16 $\alpha$  and G15 $\alpha$  still currently offer the most flexible approach for assays for orphan receptor screening based on manipulation of cellular G protein profile as these clearly can be activated by a very wide range of GPCRs." (See page 124, column 1, first paragraph.)

Milligan et al. suggest that the best approach to obtaining a universal ligand-screening system, is use of a G16 $\alpha$ /G15 $\alpha$  assay system. However, Milligan in no way suggests that the skilled artisan should alter the system of Conklin, et al. Contrary to the Examiner's allegation, it is unclear that the skilled artisan would be motivated to alter the system of Conklin, et al., which Milligan, et al. suggest is inferior to the G16 $\alpha$ /G15 $\alpha$  assay system.

Finally, Silva et al. teach a *C. elegans* G $\alpha$  protein whose sequence is 63% identical to rat Gi  $\alpha$ 2. Silva neither teaches nor suggests the existence of a nematode G $\alpha$ q protein. In fact, Silva states: "...the sequence of *C. elegans* Gpa-2 differs too much from the mammalian sequences to unambiguously assign it to one of these classes." (See page 486, column 2, last line.) Contrary to the Examiner's allegations that it would have been obvious to

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one of skill in the art at the time the invention was made to make a chimeric G $\alpha$  subunit as taught by Conklin et al. comprising a sequence from a nematode as taught by Silva et al., Silva, et al. neither teach nor suggest that nematode G proteins are interchangeable with mammalian G proteins.

Applicants point out that Silva, et al. state: "the cloning and sequencing of this gene can be the starting point of reverse genetics experiments aimed at the isolation of animals mutated in a G-protein  $\alpha$ -subunit." (See page 483, first paragraph, lines 11-13.) One skilled in the art would clearly recognize that Silva's aim is to isolate mutations in animal G-proteins. Silva et al. do not teach DNA encoding an invertebrate G $\alpha$ q protein. Silva et al. do not even teach an assay system for G proteins. Silva et al. clearly do not link their unclassified nematode G protein to any kind of utility, specifically not a universal assay utility. For the reasons stated above, applicants maintain that it would not be obvious to replace the mammalian sequence of Conklin, et al. with the invertebrate sequence of Silva, et al.

MPEP § 2142 recites:

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Applicants maintain that in light of the reasoning and arguments made hereinabove, a *prima facie* case of obviousness has not been established. First, Milligan, et al. do not provide motivation

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to alter Conklin, et al. rather, Milligan, et al. teach away from Conklin, et al. by suggesting that the G $\alpha$ 16/G $\alpha$ 15 system is superior. Second, there is no reasonable expectation of success for inserting an unknown, uncharacterized nematode G protein sequence (Silva, et al.) into the mammalian system of Conklin. Finally, neither reference teaches DNA encoding an invertebrate G $\alpha$ q protein, which isn't cured by Silva, et al. because he neither teaches G $\alpha$ q, nor does he teach an assay system.

Applicants maintain that contrary to the Examiner's allegations, the claimed invention was not obvious to the person skilled in the art at the time the application was filed. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. 103(a)\*.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

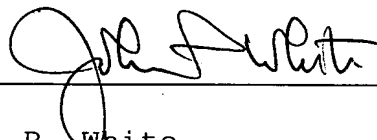
\*Applicants note for the record that the Examiner's hindsight combination of references for the purpose of a rejection under §103 underscore the lack of basis for the rejection under 35 U.S.C. §112, first paragraph. Presumably, the Examiner as a person skilled in the art has understood the claimed invention and how to assemble the technology necessary to practice applicants' claimed invention.



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No fee, other than the enclosed fee of \$930.00 (for a three month extension of time), is deemed necessary in connection with the filing of this Amendment. However, if an additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



John P. White  
Reg. No. 28,678

5/19/03  
Date



Dkt. 1795/59896/JPW/ANX

**Marked-up version of the amendments**

Additions to the text are indicated by underlining; deletions are indicated by square brackets.

**In the Claims:**

--159. (Amended) The DNA of claim 157, wherein the DNA is genomic DNA and consists [essentially] of nucleotides encoding the chimeric G protein.--